NON-TECHNICAL ABSTRACT

Adoptive Cellular Therapy of Cancer Combining Direct HLA-B7/β2-microglobulin Gene Transfer with Autologous Tumor Vaccination for the Generation of Vaccine-Primed Anti-CD3 Activated Lymphocytes

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Recent studies in animal models have demonstrated that attempts to make tumor cells look foreign to the immune system by "genetic engineering" can result in animals recognizing and eliminating these "foreign looking" tumor cells. A beneficial side-effect of this treatment is that subsequently the immune system can also recognize and reject the tumor cells that were not modified, as well as it can reject the "foreign looking" tumor cells. Our laboratory has spent the last five years examining the application of this strategy to treat patients with incurable cancer. To do this we have used an animal tumor model which resembles many human tumors in that it is very aggressive, disseminates rapidly and cannot be easily recognized by the body's immune system. Progressively growing tumors or tumor vaccines were made to look "foreign" by injecting DNA and lipid (a fatty substance which helps the DNA make the tumor look foreign) into the tumor. In some tumors this approach made the tumors shrink, while in other tumors this approach had no effect on tumor growth. However, even in animals where tumors continued to grow, there was evidence that the body had begun to recognize these tumors as foreign. In an attempt to strengthen the body's capacity to reject these tumors, immune cells (the agents responsible for tumor destruction) were removed from the body and their anti-tumor activity was turned-on or revved-up using a special stimulus (anti-CD3) and growth factor (IL-2). When these revved-up immune cells were given back to animals with cancer, they were more effective at eliminating tumor deposits than any other immune-based therapy we have used (including our "gold standard" BCG). Based on these observations we now propose to combine this approach to make tumor cells look more foreign, with our current tumor vaccine/adoptive cellular immunotherapy protocol.

Patients with renal cell carcinoma or melanoma which is judged to be incurable by standard modalities will undergo surgery to recover tumor for use as a tumor vaccine. Patients will be vaccinated with lethally irradiated (so tumor cannot grow) autologous tumor and BCG (the "gold standard") in one limb, and irradiated autologous tumor made to look foreign by adding DNA and lipid (HLA-B7/2m - VCL-1005) and either nothing, an escalating dose of DNA and lipid, or BCG in the contralateral limb. Collections of immune cells (lymph nodes) will be removed 7-14 days after vaccination to obtain immune cells (lymphocytes) for activation with a stimulus (anti-CD3 monoclonal antibody /OKT3) and subsequent expansion in growth factor (IL-2) outside of the body. After this treatment these lymphocytes will be injected into the patient along with IL-2, which will be given for 5 days. Three patients will be treated in each of 6 groups for a total of 18 patients. The toxicity and immunologic effects of treatment will be monitored.